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Ozone Exposure, Outdoor Physical Activity, and Incident Type 2 Diabetes in the SALSA Cohort of Older Mexican Americans

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Background: Type 2 diabetes is a leading contributor to the global burden of morbidity and mortality. Ozone (O_3) exposure has previously been linked to diabetes.

Objective: We studied the impact of O_3 exposure on incident diabetes risk in elderly Mexican Americans and investigated whether outdoor physical activity modifies the association.

Methods: We selected 1,090 Mexican American participants from the Sacramento Area Latino Study on Aging conducted from 1998 to 2007. Ambient O_3 exposure levels were modeled with a land-use regression built with saturation monitoring data collected at 49 sites across the Sacramento metropolitan area. Using Cox proportional hazard models, we estimated the risk of developing incident diabetes based on average O_3 exposure modeled for 5-y prior to incident diabetes diagnosis or last follow-up. Further, we estimated outdoor leisure-time physical activity at baseline and investigated whether higher vs. lower levels modified the association between O_3 exposure and diabetes.

Results: In total, 186 incident diabetes cases were identified during 10-y follow-up. Higher levels of physical activity were negatively associated with incident diabetes [hazard ratio (HR) = 0.64 (95% CI: 0.43, 0.95)]. The estimated HRs for incident diabetes was 1.13 (95% CI: 1.00, 1.28) per 10-ppb increment of 5-y average O_3 exposure; also, this association was stronger among those physically active outdoors [HR = 1.52 (95% CI: 1.21, 1.90)], and close to null for those reporting lower levels of outdoor activity [HR = 1.04 (95% CI: 0.90, 1.20), $p_{interaction} = 0.01$].

Conclusions: Our findings suggest that ambient O_3 exposure contributes to the development of type 2 diabetes, particularly among those with higher levels of leisure-time outdoor physical activity. Policies and strategies are needed to reduce O_3 exposure to guarantee that the health benefits of physical activity are not diminished by higher levels of O_3 pollution in susceptible populations such as older Hispanics. https://doi.org/10.1289/EHP8620

Introduction

Type 2 diabetes is a complex and chronic metabolic disorder caused by insulin resistance and beta cell dysfunction (Stumvoll et al. 2005). Type 2 diabetes has become a growing global and national public health concern and increases the risk of several adverse health outcomes, such as cardio- and cerebrovascular and neurodegenerative diseases (American Diabetes Association 2014). In the United States, the prevalence of Type 2 diabetes is higher among Hispanics compared with non-Hispanic Whites. It has been estimated that in 2018 the prevalence was ∼14.7% among Hispanic adults and ∼11.9% among non-Hispanic Whites (CDC 2020). Among those 65–74 years of age, the prevalence reached 33.8% in Hispanics and 17.6% in non-Hispanic Whites; and among those ≥75 years of age, 30.6% and 18.8% in Hispanics and non-Hispanic Whites, respectively (https://gis.cdc.gov/grasp/diabetes/diabetesatlas.html). Although development of diabetes has typically been related to obesity and physical inactivity, its etiology is complex and heterogeneous. More recently it has been suggested that environmental risk factors such as air pollution may also play a major role (Yang et al. 2020).

Despite great improvements in air quality control, ozone (O_3) still remains a major concern for public health in the United States, especially in California. As a secondary gaseous air pollutant formed from traffic-related precursors under the influence of sunlight, tropospheric O_3 concentrations have continuously increased in the last century, especially in areas downwind of urban centers with dense populations (Parrish et al. 2012) and high volumes of traffic. O_3 has been associated with a range of adverse health outcomes in observational studies, including cardiopulmonary diseases (Jerrett et al. 2009; Lim et al. 2019) and metabolic disorders (Hu et al. 2015; Jerrett et al. 2017).

The general health benefits of physical activity are well known. There is growing evidence that adequate physical activity, such as from recreational activities, protects against cardiovascular, metabolic, and neurodegenerative disorders (Blair 2009; Inoue et al. 2020; Paul et al. 2019; Shih et al. 2018; Williams 2009). During exercise, a number of physiologic changes occur, including an increase in the inhalation rate or depth, increasing the amount of air pollution entering the lower airways with potentially adverse impacts such as inflammatory responses and oxidative stress (Araneda et al. 2021; Morse 2005; Nicolò et al. 2018). Thus, the beneficial effects that outdoor physical activities have on human health may have to be weighed against the detrimental impacts of air pollution in areas affected by high pollution levels, such as the Sacramento area of California.

There is ample evidence for an association between air pollution such as particulate matter (PM) and nitrogen oxides (NO_x) and diabetes (Andersen et al. 2012; Brook et al. 2008; Coogan et al. 2012; Krämer et al. 2010; Pearson et al. 2010; Puett et al. 2011; Raaschou-Nielsen et al. 2013). Recently, researchers

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started to investigate the impact of O_3 on diabetes, including diabetes-related mortality (Lim et al. 2018; Zanobetti and Schwartz 2011; Zúñiga et al. 2016) and gestational diabetes (Hu et al. 2015; Pan et al. 2017; Robledo et al. 2015). However, there are few longitudinal studies investigating the role of O_3 exposure in diabetes development (Jerrett et al. 2017; Li et al. 2018; Renzi et al. 2018). Mexican Americans, the fastest growing segment of the U.S. population (U.S. Census Bureau 2018), have a high prevalence of diabetes (Aguayo-Mazzucato et al. 2019) and are also among the most highly air pollution exposed populations in California (OEHHA 2018). Yet, thus far we are not aware of any studies that have explored the relationship between O_3 exposure and diabetes or evaluated whether outdoor physical activity modifies associations between O_3 and diabetes in this population. Thus, the objective of this study was to investigate *a*) whether exposure to O_3 is associated with the risk of incident diabetes; and *b*) whether higher outdoor physical activity levels modify this association among older Mexican Americans enrolled in the Sacramento Area Latino Study on Aging (SALSA) study.

Methods

All procedures described here were approved by the Institutional Review Boards of the Universities of California, San Francisco, Los Angeles, and Davis; the University of North Carolina; and the University of Michigan. All participants provided written informed consent.

Study Population

Study participants were enrolled in the SALSA study, a longitudinal cohort of older Mexican Americans who lived in the Sacramento area. The recruitment was conducted in the Sacramento metropolitan area and surrounding suburban and rural counties, with a percentage of old-age (≥60 years of age) Hispanic residents of at least 5% based on 1990 and 1998 U.S. Census information (Haan et al. 2003; Mungas et al. 2018). Participants were contacted via mail, telephone, and door-to-door neighborhood enumeration. Participants who *a*) were ≥60 years of age; *b*) resided in the six counties of the California Sacramento Valley; *c*) self-identified as Latinos; *d*) were Spanish or English speakers; and *e*) were living in a noninstitutionalized setting were eligible to be enrolled in the study. Cognitive function at baseline was not an eligibility criterion for inclusion in the study. Among those eligible and contacted, 83.5% agreed to participate in the study. In total, 1,789 participants were recruited at baseline (1998 and 1999). Participants were interviewed in their homes at baseline, and follow-up home visits were conducted every 12–15 months until the end of 2007, for a maximum of seven follow-up visits. Between home visits, a 10-min phone call every 6 months was performed until the end of the study to update participants' contact information, health status, and medication information. The average annual attrition rate from mortality and loss to follow-up was 2.6% and 2.3%, respectively. The average length of follow-up was 6.5 y, with a maximum of 10 y (Haan et al. 2003). Those who *a*) did not participate in the interview at baseline ($n=3$); *b*) lived too far from traffic sources to generate O_3 exposure measures ($n=3$); *c*) already had diabetes at baseline ($n=585$); *d*) did not provide information of diabetes status at baseline ($n=7$); *e*) did not provide information about outdoor recreational physical activities ($n=59$); or *f*) did not have any follow-up visits ($n=42$) were excluded, leaving 1,090 participants for analysis (Figure 1).

Ozone Exposure Assessment

The O_3 concentrations were estimated based on a land-use regression (LUR) model. To build this model, we conducted two

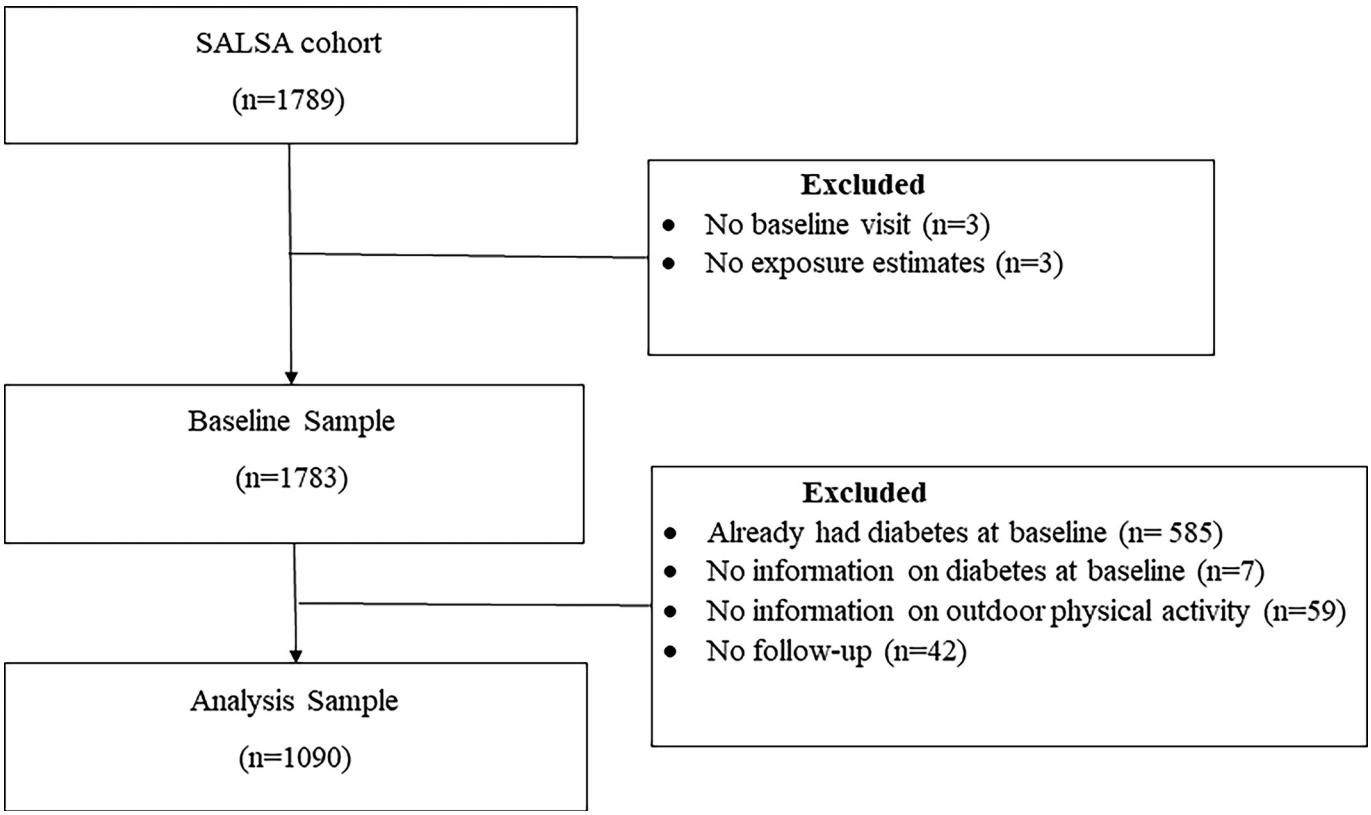

Figure 1. Flow chart of study population, Sacramento Area Latino Study on Aging (SALSA), 1998–2007.

O_3 saturation monitoring campaigns in the Sacramento metropolitan area at 49 sites, one in late spring (20 May 2016–3 June 2016) and one in winter (2 December 2016–16 December 2016). The mean and standard deviation (SD) of the measured O_3 concentrations were 21.5 and 4.7 ppb, respectively. For LUR modeling, we applied the deletion/substitution/addition (D/S/A) algorithm to generate an annual prediction model (Beckerman et al. 2013; Su et al. 2015). More details can be found elsewhere (Su et al. 2020). Briefly, the D/S/A algorithm is an aggressive model search algorithm that follows three steps—*a*) deletion (which removes a term from the model); *b*) substitution (which replaces one term with another); and *c*) addition (which adds a term to the model)—based on existing terms in the current best model in order to iteratively generate polynomial generalized linear models. The LUR model was developed specifically for the Sacramento metropolitan area using saturation monitoring data we collected in 2016, with the input of both buffered (i.e., land cover and traffic) and nonbuffered data sources (i.e., distance to coast and roadways). Because we had only 1 y of O_3 data, the LUR model was built without using repeated measures of individual air quality monitoring stations for the modeling process. The O_3 concentration surface throughout the Sacramento area was first generated at a spatial resolution of 30×30 m (Figure S1) and then averaged within a 1-km radius using zonal statistics through the mean function to account for regional impact due to temperature effects (Figure 2). The final LUR model had an adjusted prediction power (adjusted R^2) of 76% (Miles 2014).

Each residential home address was first assigned the modeled annual pollutants concentrations for O_3 in the reference year 2016 (Sacramento-specific surface) (Figure 2; Figure S1). There were eight U.S. Environmental Protection Agency (EPA) air quality monitoring sites for O_3 in total in the Sacramento area. The data (maximum 8-h daily O_3 concentration) from the nearest monitoring site with an effective annual measurement (at least 75% completeness in each quarter of a year) for a specific year was then used (U.S. EPA 2006), along with the modeled O_3 data, to estimate the annual exposures for the years 1988–2007 at each

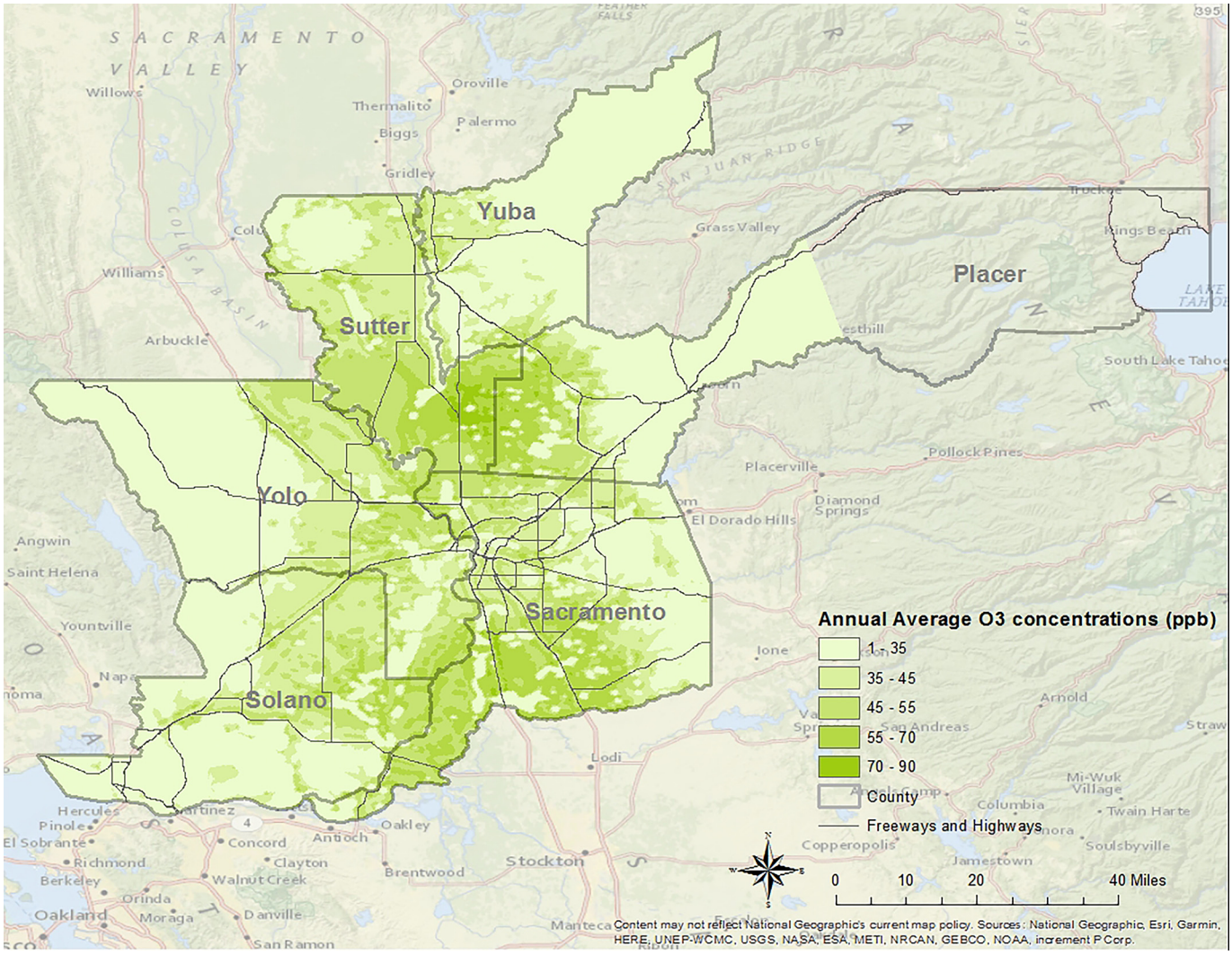

Figure 2. Estimated annual average ozone (O_3) concentration surface in the Sacramento area in 2016 with a spatial resolution of 1×1 km, Sacramento Area Latino Study on Aging (SALSA, 1998–2007). Ambient O_3 exposure levels were modeled with a land-use regression built with saturation monitoring data collected at 49 sites across the Sacramento metropolitan area. The base map was developed by National Geographic and ESRI and reflects the distinctive National Geographic cartographic style in a multiscale reference map of the world. The map was authored using data from a variety of leading data providers, including Garmin, HERE Technologies, the United Nations Environment Programme's World Conservation Monitoring Centre, the National Aeronautics and Space Administration, the European Space Agency, and the U.S. Geological Survey, and others. County boundary data was taken from the California Open Data Portal (https://data.ca.gov/dataset/ca-geographic-boundaries).

residential address. For a residential address of location i at year t with reference year d, the exposure value $E^j_{i,d,t}$ for pollutant j (here $j = O_3$) were calculated as follows:

$$E^j_{i,d,t} = C^j_{d,i} \times \frac{C^j_{m,t}}{c^j_{m,d}},$$

where $C^j_{d,i}$ is the modeled concentration of pollutant j at location i in reference year d; $C^j_{m,t}$ is the measured concentration of pollutant j at the U.S. EPA monitor m that is closest to location i in year t; $c^j_{m,d}$ is the concentration of pollutant j at the nearest U.S. EPA monitor m in reference year d.

Diabetes

During the visits at baseline and follow-up, diabetes was defined as the presence of any one of the three following conditions: *a*) self-reported physician diagnosis (participants were asked if a physician had ever told them that they had diabetes); *b*) antidiabetic medication use; or *c*) a fasting glucose level >126 mg/dL (7.0 mmol/L). The fasting glucose level was measured at baseline and at almost all follow-up visits (first, third, fourth, fifth, and sixth follow-up visits) using the Cobas Mira Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN) (Mayeda et al. 2015), and participants were required to have had no caloric intake for ≥8 h before the tests. Diabetes medication use was recorded after a medicine cabinet inventory at each home visit and was updated during intermittent phone calls [classified according to the Centers for Disease Control and Prevention Ambulatory Care Drug Database (http://www2.cdc.gov/drugs)]. At baseline, neither the date of physician diagnosis nor the start date of medication use was queried, but diabetics identified at baseline were excluded from the analyses. After each exam, participants were provided with a blood test result report for their health care provider. During study visits, >97% of participants whose fasting blood glucose was >126 mg/dL also self-reported a previous physician diagnosis of diabetes; ~70% of participants with a self-reported diagnosis were taking medication, and everyone taking medications reported a physician diagnosis. Thus, the agreement between fasting glucose level and self-reported diagnosis and medication use was relatively high in our study and confirmatory of the diagnosis.

Incident cases of diabetes were participants without diabetes at baseline who developed diabetes during follow-up. As the date of an incident diabetes diagnosis, we chose the home visit date during which the condition was first recorded according to our criteria. Given that all participants were already ≥60 years of age, most incident cases identified were most likely type 2 diabetes (Mayeda et al. 2015; Shih et al. 2018). In the following, we use "diabetes" to hereafter refer to type 2 diabetes.

Outdoor Leisure-Time Physical Activities

Participants were asked to report the average number of hours they spent on 18 different types of activities during a regular week at baseline (for example, participants were asked, "How many hours per week do you do garden or yardwork?") without querying leisure-time or nonoccupational activities specifically. Among the 18 activities, we selected 7 physical activities (doing yardwork, taking walks to other places such as grocery shops, swimming or working out, dancing, hunting or camping or boating, golf or other moderate exercise games, or walking around the neighborhood) that are likely to be performed outdoors. Each activity was assigned a metabolic equivalent of task (MET) according to the Compendium of Physical Activities (Ainsworth et al. 2000), and the MET value was multiplied by the reported time (hours/week) spent performing the activity (MET-hours/week) for each activity. Finally, we summed the MET-hours/week values for the 7 activities to generate a cumulative outdoor physical activity measure.

Other Covariates

Demographic information including birthplace (Mexico, the United States, or other), years of education, and longest held occupation during the lifetime (nonmanual labor, manual labor, or other) were also collected at baseline. At each interview, participants also reported household income, marital status, smoking, health status, and medication use. Body mass index (BMI; in kilograms/meter squared) was calculated according to standing height and weight collected by trained interviewers (Shih et al. 2018). Activities of daily living (ADL) was derived on a self-reported multi-format scale (0, independent; 1, supervision; 2, limited assistance; 3, extensive assistance; 4, total dependence; 7, activity occurred only once or twice; and 8, activity did not occur) referring to six activities, including bathing, dressing, eating, transferring, toileting, and continence (Inoue et al. 2020). An indicator for urban or rural residential location was generated relying on U.S. Census tract 2000 information (U.S. Department of Agriculture Economic Research Service 2019). Neighborhood socioeconomic status (NSES) is represented as a score ranging from 1 to 5 (low to high NSES) depending on six 2000 U.S. Census (https://www.census.gov/programs-surveys/decennial-census/decade.2000.html) estimates: percentage of *a*) individuals ≥25 years of age without a high school diploma; *b*) individuals below the poverty limit; *c*) individuals ≥16 years of age who had been in the workforce at one time but are unemployed; *d*) households owning their home; *e*) vacant housing units; and *f*) median number of rooms in a household (Yost et al. 2001).

Details for how we generated local traffic-related NO_x and noise estimates have been described elsewhere (Yu et al. 2020). Briefly, local traffic-related NO_x level at baseline was assessed using the California Line Source Dispersion Model (version 4; CALINE4) (Benson and Pinkerman 1989; Wu et al. 2009, 2016) with the input of 2002 traffic data and meteorology data from the California State Department of Transportation and the California Air Resources Board Air Quality and Meteorological Information System (https://www.arb.ca.gov/aqmis2/metselect.php), respectively. Traffic-related noise exposure was estimated using the SoundPLAN (version 8.0; NAVCON, Fullerton, CA, USA) software package, which is implemented with a noise prediction model; that is, the Federal Highway Administration Traffic Noise Model that uses annual average daily traffic data from Metropolitan Planning Organizations. Similar to the Sacramento-specific 2016 LUR modeling for O_3, we also modeled LUR-based nitrogen dioxide (NO_2) concentration (mean ± SD) for the Sacramento area at 69 sites (6.1 ± 9.4 ppb). Similar predictors as used for O_3 modeling went into the D/S/A modeling framework for NO_2 predictions, and the model had an adjusted prediction power of 60%. Fine particulate matter with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$) estimates were also derived with the D/S/A LUR modeling technique based on 110 unique governmental monitoring stations located throughout California (10.7 ± 3.9 $\mu g/m^3$), with an adjusted prediction power of 64%. The residential exposures for NO_2 and $PM_{2.5}$ for the years 1988–2013 were estimated in a way similar to that estimated for O_3 exposures, using the same equation and in which the pollutant j was changed to NO_2 or $PM_{2.5}$, respectively. The University of Idaho Gridded Surface Meteorological Dataset (GRIDMET; https://developers.google.com/earth-engine/datasets/catalog/IDAHO_EPSCOR_GRIDMET) was used to generate the temperature for the study region.

Statistical Methods

Cox proportional hazards regression models with calendar time as the underlying time scale were used to estimate the impact of O_3 exposures for each calendar year on incident diabetes. Participants were censored at their last date of contact only if they did not return for a follow-up visit or at the time of death before 31 December 2007. Mortality data was collected through interviews with family members when we did not reach participants for annual follow-up visits or during the interim 6-month phone calls, by reviewing online death notices, checking the Social Security Death Index, the National Death Index, and California state vital statistics data.

Time-varying O_3 exposures were calculated as the O_3 levels averaged over the 5 calendar years prior to the onset of an event for everyone in the risk set at the event time and treated as continuous variables scaled by the interquartile ranges (IQRs). Because the effect estimates for the first three quartiles of physical activity level and diabetes incidence were very similar (data not shown), we merged these into one category to increase analysis power; thus, outdoor leisure-time physical activity was dichotomized into a low (outdoor physically inactive) and a high (outdoor physical active) level comparing the highest to the first three quartiles (<74.5 vs. ≥74.5 MET-h/wk) among those who reported engaging in at least one of the seven selected activities, based on the distribution observed for the entire SALSA cohort (Table S1).

To examine the impact of O_3 exposure on diabetes, we selected covariates for adjustment based on the prior literature for O_3 exposures and diabetes (Jerrett et al. 2017; Renzi et al. 2018) and included demographic-socioeconomic factors (baseline age, sex, years of education, longest held occupation, household income, NSES, and marital status) and lifestyle factors (outdoor physical activity, smoking status), BMI, ADL, as well as time-invariant traffic-related NO_x (CALINE4) and noise (SoundPLAN) exposures estimated for the baseline year and the 5-y prior to baseline averages for the LUR-derived NO_2 and $PM_{2.5}$ and for temperature (GRIDMET). NO_x, noise, NO_2, $PM_{2.5}$, and temperature were treated as continuous variables and standardized according to their IQRs, respectively. Baseline years of education, BMI, and ADL were also treated as continuous variables and sex, longest held occupation, household income, outdoor physical activity, smoking status, marital status, and NSES as categorical variables, as shown in Table 1.

We first estimated effects from a model adjusting only for baseline age, sex, and years of education. We then added longest held occupation and household income, outdoor physical activity, and smoking status (which are the major risk factors for cardiometabolic diseases), as well as an NSES indicator, considering that the O_3 estimates vary spatially. To address the potential confounding by other air pollutants and temperature, we also coadjusted one by one for local traffic-related NO_x and noise and for total NO_2 and $PM_{2.5}$ concentrations, as well as for temperature, individually. We also used a restricted cubic spline model to describe the dose–response relationship between O_3 exposure and diabetes risk. Various averaging periods were also constructed to investigate the associations between time-varying O_3 exposure in different windows and the risk of diabetes, including 1-, 2-, 3-, and 4-y averages prior to the onset of an event for everyone in the risk set at the event time. In addition, the 5-y average O_3 exposure prior to baseline year was used to examine the relationship between O_3 and diabetes. We also repeated the analyses using the O_3 estimates generated from the unsmoothed surface with 30- × 30-m resolution.

We further examined the association between O_3 and diabetes stratified by outdoor leisure-time activity levels and by including an interaction term between outdoor leisure-time activity and O_3 exposure into the model. As in our main analyses, the O_3 exposure and outdoor leisure-time activity levels were treated as a continuous and a categorical variable (fourth vs. lower three quartiles), respectively, and a $p_{interaction}$ term was derived.

In sensitivity analyses, we additionally adjusted for baseline BMI, marital status, and ADL, considering that these factors might influence lifestyle or where participants live and thus act as

Table 1. Summary of characteristics of the participants at baseline used for incidence analyses, Sacramento Area Latino Study of Aging, 1998–2007.

Characteristics {mean ± SD or *N* (%)}	Total ($n = 1,090$)	Diabetes	
		No-event ($n = 904$)	Event ($n = 186$)
Baseline age [y (mean ± SD)]	70.5 ± 6.9	70.8 ± 7.1	69.3 ± 5.9
Sex [*N* (%)]			
Male	446 (40.9)	363 (40.2)	83 (44.6)
Female	644 (59.1)	541 (59.9)	103 (55.4)
Years of education (mean ± SD)	7.5 ± 5.3	7.5 ± 5.3	7.6 ± 5.4
Residential area [*N* (%)]			
Urban	954 (87.5)	785 (86.8)	169 (90.9)
Rural	136 (12.5)	119 (13.2)	17 (9.1)
Longest held occupation [*N* (%)]			
Nonmanual	232 (21.3)	197 (21.8)	35 (18.9)
Manual	650 (59.6)	540 (59.7)	110 (59.1)
Other (housewives and unemployed)	196 (18.0)	158 (17.5)	38 (20.4)
Missing	12 (1.1)	9 (1.0)	3 (1.6)
Marital status [*N* (%)]			
Single/never married	35 (3.2)	29 (3.2)	6 (3.2)
Married/living with someone as a spouse	636 (58.3)	519 (57.4)	117 (62.9)
Widowed	276 (25.3)	231 (25.6)	45 (24.2)
Divorced	111 (10.2)	98 (10.8)	13 (7.0)
Separated	32 (2.9)	27 (3.0)	5 (2.7)
Household Income {$/month [*N* (%)]}			
<1,000	465 (42.7)	386 (42.7)	79 (42.5)
1,000–1,499	220 (20.2)	182 (20.1)	38 (20.4)
1,500–1,999	121 (11.1)	108 (12.0)	13 (7.0)
2,000–2,499	108 (9.9)	90 (10.0)	18 (9.7)
≥2,500	161 (14.8)	125 (13.8)	36 (19.4)
Missing	15 (1.4)	13 (1.4)	2 (1.1)
NSES [*N* (%)][a]			
Low (NSES = 1)	352 (32.3)	299 (33.1)	53 (28.5)
Low-middle/middle (NSES = 2, 3)	621 (57.0)	515 (57.0)	106 (57.0)
Middle-high/high (NSES = 4, 5)	117 (10.7)	90 (10.0)	27 (14.5)
Baseline smoking status [*N* (%)]			
Never/nonsmoker	515 (47.3)	441 (48.8)	74 (39.8)
Former smoker	438 (40.2)	339 (37.5)	99 (53.2)
Current smoker	137 (12.6)	124 (13.7)	13 (7.0)
Baseline outdoor leisure-time physical activity [*N* (%)][b]			
Higher level	263 (24.1)	230 (25.4)	33 (17.7)
Lower level	827 (75.9)	674 (74.6)	153 (82.3)
Baseline BMI (mean ± SD)	29.2 ± 5.6	28.9 ± 5.7	30.6 ± 4.9
ADL summary score (mean ± SD)	0.5 ± 2.1	0.5 ± 2.2	0.5 ± 1.7
5-y Average O_3 prior to baseline [ppb (mean ± SD)]	46.0 ± 11.2	45.7 ± 10.9	47.6 ± 12.5

Note: There were no observations with missing data for the continuous variables. ADL, activities of daily living; BMI, body mass index; MET, metabolic equivalent of task; NSES, neighborhood socioeconomic status; O_3, ozone; SD, standard deviation.

[a]NSES is represented as a score ranging from 1 to 5 (low to high NSES) depending on six 2000 U.S. Census (https://www.census.gov/programs-surveys/decennial-census/decade.2000.html) estimates: percentage of *a*) individuals aged ≥25 y without a high school diploma, *b*) individuals below the poverty limit, *c*) individuals aged ≥16 y who had been in the workforce at one time but are unemployed, *d*) households owning their home, *e*) vacant housing units, and *f*) median number of rooms in a household.

[b]Seven physical activities (doing yardwork, taking walks, swimming or working out, dancing, hunting or camping or boating, golf or other moderate exercise games, walking around the neighborhood) that are likely to be performed outdoors were selected to be included in the measure of outdoor leisure-time physical activity level, the MET value was multiplied by the reported time (hours/week) spent performing the activity (MET-hours/week) for each activity and then summed up to generate a cumulative outdoor leisure-time physical activity measure, dichotomized using the cutoff point of 74.5 MET-h/wk.

potential confounders. We also repeated analyses using stratified Cox regression models with different age groups (<70, 70–80, ≥80 years of age) as strata. Furthermore, we applied the O_3 estimates generated by the U.S. EPA Bayesian space–time Downscaler model and repeated the analyses. Last, to examine whether the increased risk of diabetes due to O_3 exposure among those with higher outdoor leisure-time activities might simply reflect an effect of higher physical activity in general, we repeated the analyses for the 10 major activities likely performed indoors (Table S1), dichotomizing indoor activity at the same cutoff point as outdoor activity (<74.5 vs. ≥74.5 MET-h/wk).

SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all the analyses. Complete-case analyses were also performed.

Results

The average age of study participants was 70 y at baseline, and they had on average received 7.5 (±5.3) y of formal education (Table 1). Less than half (41%) were men and 87.5% lived in an urban area. Approximately 60% of the participants held a manual labor job during most of their lifetime, 43% reported a monthly household income of <$1,000. Compared with those who did not develop diabetes during follow-up, participants who developed diabetes were more likely to be former smokers and had a higher BMI and were less likely to be physically active outdoors. The mean value for the reported participation in outdoor physical activity was 57.2 (±52.7) MET-h/wk at baseline among those who reported engaging in at least one of the seven selected activities (Table S1). Compared with the 827 participants who were classified as having lower levels of leisure-time outdoor physical activities (<74.5 MET-h/wk), participants with a higher level of leisure-time outdoor physical activity (≥74.5 MET-h/wk, $n = 263$) were more likely to be men, to have worked in manual labor jobs as their longest held occupation, and to be married (Table S2). The 5-y average concentration of O_3 at the residence prior to baseline year was ∼46 (±11.2) ppb (Table 1), and annual average O_3 concentrations during the study period ranged from 43 to 50 ppb (Table S3). Pearson's correlation coefficients for O_3 and other air pollutants at baseline ranged from –0.23 (for NO_2) to –0.06 (for $PM_{2.5}$) (Table S4).

During a maximum of 10 y of follow-up, each participant on average completed ∼5 follow-up visits and ∼10 phone calls. A total of 177 participants died without a diabetes diagnosis during follow-up; among the 260 participants who did not return for the last follow-up visit, 85% finished at least one follow-up visit. The average person-time accrued for cases was ∼4.6 (range: 0.9–9.1 y), and ∼5.8 y for noncases (range: 0.1–9.7 y). In total, 186 participants developed incident diabetes. Among them, 17% of the cases were identified only by the fasting glucose test result, and 11% by self-report diagnosis and medication use. A restricted cubic spline model suggested that hazard ratios (HRs) for incident diabetes are linear with increasing O_3 exposure (Figure S2). Based on the Cox model, the risk of developing diabetes increased by 13% {HR = 1.13 [95% confidence interval (CI): 1.00, 1.28]} per 10-ppb (IQR) per unit increase in O_3, after adjusting for demographic-socioeconomic and lifestyle factors (Table 2). The effect estimates for O_3 and onset of diabetes remained similar when we further adjusted for BMI, marital status, ADL, and other pollutants, including NO_x, NO_2, $PM_{2.5}$, noise, and temperature, respectively. In the models where we also individually coadjusted O_3 exposure estimates for local traffic-related NO_x or noise, total NO_2 or $PM_{2.5}$ concentrations, exposure to $PM_{2.5}$ or NO_2 were also positively associated with incident diabetes [HR = 1.20 (95% CI: 1.03, 1.40) per 1.9 $\mu g/m^3$ increase in $PM_{2.5}$; HR = 1.02 (95% CI: 0.98, 1.05) per 6.1-ppb increase in NO_2], but no associations between traffic-related NO_x or noise exposures and diabetes were observed (Table S5). Repeating analyses for the O_3 estimates from the 30- × 30-m resolution surface, results did not change much [HR = 1.11 (95% CI: 1.01, 1.22)] (Table S6). When using the O_3 estimates derived from the U.S. EPA Downscaler model, the association between O_3 and diabetes attenuated [HR = 1.07 (95% CI: 0.93, 1.24) per IQR (1.5 ppb) increase in O_3] (Table S6). The results remained similar [HR = 1.20 (95% CI: 1.02, 1.41) per IQR (9.6 ppb) increase] when using the 5-y average O_3 exposure prior to baseline (Table S7). The associations between incident diabetes and O_3 exposure for different averaging periods (1- to 4- y average) were similar (Table S8). Our results changed only minimally for the stratified Cox regression model with different age groups as strata (Table S9).

Table 2. Effect estimates (and 95% CIs) from Cox models for O_3 exposure on incident diabetes.

	5-y Average O_3, per 10-ppb increase	
Model	HR	95% CI
1[a]	1.14	1.00, 1.29
2[b]	1.13	1.00, 1.28
3[c]	1.10	0.98, 1.26
4[d]	1.14	1.00, 1.30
5[e]	1.13	1.00, 1.20
6[f]	1.12	0.98, 1.27
7[g]	1.13	1.00, 1.29
8[h]	1.13	0.99, 1.29

Note: The time-invariant traffic-related NO_x and noise exposures, NO_2, $PM_{2.5}$ exposure, and temperature were treated as continuous variables and standardized according to their respective IQRs; baseline age, years of education, BMI, and ADL were also treated as continuous variables. Sex, longest held occupation, household income, outdoor physical activity, smoking status, marital status, NSES were used as categorical variables. In Model 1, there were 1,090 observations and 186 cases, with 6,087 person-years in total; in Models 2–8, there were 1,075 observations and 184 cases, with 6,022 person-years in total. ADL, activities of daily living; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NO_2, nitrogen dioxide; NO_x, nitrogen dioxides; NSES, neighborhood socioeconomic status; O_3, ozone; $PM_{2.5}$, fine particulate matter (PM with an aerodynamic diameter of ≤2.5 μm).
[a]Adjusted for baseline age, sex, and education.
[b]Primary model, adjusted for covariates in Model 1 plus longest held occupation, NSES, outdoor physical activity, smoking status, and household income at baseline.
[c]Adjusted for covariates in Model 2 plus BMI, marital status, and ADL.
[d]Adjusted for covariates in Model 2 plus traffic-related NO_x.
[e]Adjusted for covariates in Model 2 plus NO_2 exposure.
[f]Adjusted for covariates in Model 2 plus $PM_{2.5}$ exposure.
[g]Adjusted for covariates in Model 2 plus traffic-related noise.
[h]Adjusted for covariates in Model 2 plus temperature.

Overall, higher levels of leisure-time outdoor physical activity were negatively associated with the incidence of diabetes [HR = 0.64 (95% CI: 0.43, 0.96)]. In the model that contained an interaction term between outdoor physical activity (fourth vs. lower three quartiles) and O_3 exposure, the O_3-related risk of developing diabetes was 1.5 times higher in the higher-activity group relative to the lower-activity group ($p_{interaction} = 0.01$) (Figure S3). The estimated HR for incident diabetes among those physically active outdoors was 1.52 [HR = 1.52 (95% CI: 1.21, 1.90)] per IQR (10 ppb) increase in average 5-y O_3 concentration compared with 1.04 (95% CI: 0.90, 1.20) for those with lower levels of outdoor physical activity (Table 3). When instead stratifying by lower or higher indoor physical activity, we did not find any evidence for effect measure modification of the O_3 association by indoor activity with incident diabetes [indoor physical activity <74.5 MET-h/wk: HR = 1.36 (95% CI: 0.72, 2.59) per 10-ppb increase in O_3; indoor physical activity ≥74.5 MET-h/wk: HR = 1.12 (95% CI: 0.97, 1.27) per 10-ppb increase in O_3] (Table S10).

Discussion

During the 10-y of follow-up in the SALSA study, O_3 exposure was associated with an increased risk of developing incident diabetes among Mexican Americans living in the Sacramento area.

Table 3. Effect estimates (and 95% CIs) from Cox models for O_3 exposure on incident diabetes, stratified by outdoor leisure-time physical activity level.

Outdoor physical activity	N	Cases (n)	5-y Average O_3, per 10-ppb increase [HR (95% CI)]
Lower level	827	153	1.04 (0.90, 1.20)
Higher level	263	33	1.52 (1.21, 1.90)
$p_{interaction}$			0.01

Note: Model was adjusted for baseline age, sex, education, longest held occupation, NSES, smoking status, and household income. Baseline age and years of education were treated as continuous variables. Sex, longest held occupation, household income, outdoor physical activity, smoking status, marital status, and NSES were used as categorical variables. The estimated coefficient (standard error) of interaction is 0.38 (0.13). The outdoor physical activity level cutoff was 74.5 MET-h/wk. The outdoor physical activity is an estimate based on leisure-time activities that were assumed to be performed mostly outdoors. CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; O_3, ozone; NSES, neighborhood socioeconomic status.

The effect estimates changed little after inclusion of other pollutants in the models. Higher outdoor leisure-time physical activity was negatively associated with the incidence of diabetes. Furthermore, the association between O_3 and incident diabetes was stronger among participants classified as having higher levels of leisure-time outdoor physical activity than among those classified as having lower levels.

Growing evidence indicates that ambient air pollution contributes to the development of diabetes (Brook et al. 2013; Chen et al. 2013; Coogan et al. 2012; Park et al. 2015; Puett et al. 2011); but few longitudinal studies to date have investigated the impact of O_3 on diabetes. One of these is a large cohort of 45,231 women (on average, ~38 years of age at recruitment) enrolled in the Black Women's Health Study with 16 y of maximum follow-up that reported a HR for incident diabetes of 1.18 (95% CI: 1.04, 1.34) per 6.7-ppb increase in O_3 exposure (Jerrett et al. 2017). Another study consisting of 410,267 women assembled through the Bureau of Vital Statistics and Office of Health Statistics and Assessment, Florida Department of Health, estimating the risk of gestational diabetes reported an odds ratio of 1.18 (95% CI: 1.15, 1.21) per 5-ppb increase in O_3 exposure during pregnancy (Hu et al. 2015). In addition to diabetes incidence, previous studies examined the potential influence of O_3 exposure on metabolic biomarkers such as hemoglobin A1c (Lanzinger et al. 2018) and fasting glucose levels (Li et al. 2018). However, these were mostly cross-sectional studies with short-term O_3 exposure and do not represent longer-term influences of O_3 on chronic health outcomes. Although epidemiological evidence is limited and inconsistent, animal experiments suggest that O_3 exposures may induce insulin resistance. For example, comparing O_3-exposed Wistar rats to rats breathing clean air, 16 h of O_3 exposure increased the rats' fasting glucose levels by 23%, also whole-body insulin resistance was induced and oxidative stress biomarkers such as 4-hydroxy-2-nonenal, 4-hydroxy-2-hexenal, and carbonyls were found to be increased (Vella et al. 2015). Another animal study treating Brown Norway rats demonstrated that glucose intolerance and hyperglycemia were caused in rats of all ages after 12 h of O_3 exposure (1.0 ppm, 6 h/d for 2 d) (Bass et al. 2013). These experimental results indicate possible mechanisms such as oxidative stress induced by O_3 inhalation, followed by systemic pro-inflammatory and autonomic responses via translocation of pro-oxidant molecules from the pulmonary alveolar fluid into systemic circulation (Vella et al. 2015), similar to what has been shown for other air pollutants (Rao et al. 2015).

Physical activity is well known and widely recognized for its health benefits, ranging from reduced risk of chronic diseases, including diabetes, to functional preservation during aging (Blair 2009). However, physical activity can alter the breathing frequency and tidal volume and encourage oral vs. nose breathing and thus may increase the amount of O_3 reaching the lower airways and tissues relevant for gas exchange (Morse 2005). It has been shown that the O_3-related physiologic response varies with the distribution of O_3 in the upper and lower airways, breathing patterns, and the anatomy of airways and airspaces (Ultman et al. 2004). In a study that experimentally exposed 32 male and 28 female nonsmokers to O_3 during exercise, the researchers observed that O_3 uptake efficiency was negatively related to breathing frequency, which could lead to a decreased time for O_3 absorption but positively associated with tidal volume, which drives O_3 more deeply into the lung, where O_3 can act on the airway epithelium because it is not protected by a thick mucus layer (Ultman et al. 2004). In a chamber study of 22 nonsmoking adult men, pulmonary reactivity was increased after 5-h of exercise (representative of a day of moderate to heavy work or play) even at low O_3 concentrations (Horstman et al. 1990). Thus, people engaging in physical activities outdoors while exposed might be affected adversely owing to the increased inhalation of air pollution (McConnell et al. 2002). This might explain our observation that ambient O_3 exposure contributes to the development of type 2 diabetes, particularly among those with higher levels of leisure-time outdoor physical activity.

Our results are supported by some previous studies. A cohort study of 3,535 children recruited from schools in Southern California reported a more than 3-fold increased risk of developing asthma in children who engage in intensive exercise [relative risk = 3.3 (95% CI: 1.9, 5.8)] when exposed to high O_3 concentrations, compared with those who did not engage in outdoor sports (McConnell et al. 2002). Similarly, a Hong Kong study of 821 children 8–12 years of age observed that the maximum oxygen intake was significantly lower among those who exercised in high vs. in low air pollution areas, indicating that the beneficial effect of physical activity might be impeded by air pollution (Yu et al. 2004). On the other hand, a case–control study of 24,053 Hong Kong Chinese reported that among ≥65-y-old never-exercisers (exercised <once/month) the excess risks of all-cause mortality were higher [1.75% (95% CI: 0.25%, 3.23%) per 10-$\mu g/m^3$ increase in O_3 exposure] compared with those who reported exercising (≥once/month) outdoors during the 10 y before death (Wong et al. 2007). Recently, researchers from the U.S.-based prospective Nurses' Health Study (NHS; $n = 104{,}990$, 1998–2008) also found no statistically significant interactions between $PM_{2.5}$ exposure and physical activity (overall, walking, vigorous activity) for cardiovascular disease risk and overall mortality (Elliott et al. 2020). However, the NHS focused on recreational activities such as jogging, biking, and calisthenics, and these female nurses were on average 63 years of age at the end of follow-up; that is, they were much younger than the SALSA cohort participants.

Overall, previous studies have varied greatly in study design, exposure characteristics, population, and outcomes, as well as in the types of outdoor physical activities and physical activity levels studied (Strak et al. 2010; Tainio et al. 2021). Although the evidence for the impact of air pollution and physical activity on health is mixed, physical activity has been consistently associated with a decreased risk of cardio-metabolic disease. However, breathing frequency, tidal volume, and fraction of oral breathing—which are influenced by the intensity of physical activity—will affect particle deposition and gas absorption in the respiratory tract (ICRP 2015), and might attenuate the benefits of physical activity. There are multiple physiological and behavioral mechanisms linking physical activity and air pollution, but the biologic interaction between air pollution exposure and physical activity for health outcomes is not yet well understood (Elliott et al. 2020; Tainio et al. 2021).

In coexposure models, apart from O_3 exposure, we also observed positive associations between NO_2, $PM_{2.5}$, and incident diabetes, corroborating previous studies (Bai et al. 2018; Hansen et al. 2016; Renzi et al. 2018). When we repeated the analyses using the estimates derived from the U.S. EPA Downscaler, effect estimates attenuated, possibly because the Downscaler's chemical transport model targets a 10-km grid centered of census tracts and is being calibrated through a Bayesian algorithm to the sparse government monitoring sites. Thus, it has a relatively coarse resolution and does not capture the smaller-scale variations of O_3 exposure in the Sacramento area. Although associations between 1- or 2-y annual averages for O_3 and incidental diabetes were similar to those of a 5-y average, these short-term exposure measures likely simply reflect the longer-term and not time but, rather, spatially varying exposures that influence these chronic health outcomes.

SALSA is a population-based longitudinal cohort study with repeated follow-up exams and has allowed us to study incident diabetes over a 10-y period. The longitudinal design also provided an opportunity to estimate the association between air pollution exposure, physical activity, and diabetes in in the proposed temporal sequence because prevalent diabetes might also be followed by increases in activity if physical activity is recommended by health care providers. This is one of the first studies exploring the impact of O_3 exposure on diabetes risk in Mexican Americans, a population with a high prevalence of diabetes. O_3 exposure was estimated based on the participants' residential addresses geocoded by global positioning system readings during home visits. Exposure measures were generated with an LUR model that incorporated data from two O_3 saturation monitoring campaigns we conducted across the Sacramento metropolitan area in the spring and winter of 2016 at 40 sites. These were combined with land use and meteorological data, and our model captures important air pollution sources from traffic and goods movement, wood burning, and industry. In addition, our LUR model is particularly well suited for estimating finer-scale spatial variation in these pollutants. Ambient O_3 levels increase with growing distance from roadways, and we used a 1-km smoothing approach to take regional photochemistry into account (Apte et al. 2017) when generating O_3 exposure levels for immediate neighborhoods around residences that may best represent outdoor exposure in physically active participants.

There are several limitations to be noted. O_3 exposure concentrations were assessed based on the participants' geocoded address at baseline, using an LUR model with O_3 monitoring data input from only 1 y (2016) and two seasons, and we annualized exposures using data from the nearest continuous government monitor for O_3. We lacked lifetime residential histories and we did not take into account growing population density and land use changes, thus exposure misclassification cannot be ruled out. However, in the SALSA cohort, the average length participants reported having lived at their baseline residences was 22 y and 90% remained in California throughout the study period. In addition, the spatial pattern of traffic in the Sacramento area did not change much during the study period (Kang et al. 2012; Paul et al. 2020). Thus, our exposure measures based on the baseline addresses likely characterize long-term spatial O_3 distribution around each participants' residence before and throughout the study period. In addition, we conducted the monitoring campaigns in spring and winter, thus it is possible that the absolute annual average concentrations are underestimated because of a lack of summer measurements. Given that SALSA enrolled participants who were $\geq$60 years of age at baseline, it is reasonable to assume that most of their outdoor physical activity took place in close proximity to their residence, which our model represents well given its 1- $\times$ 1-km resolution. Some participants might have developed diabetes between study visits, and some might not have been diagnosed owing to limited health care access. However, fasting glucose was measured at each study visit and we assigned the visit date that triggered the diabetes classification as the event onset date, thus the mismeasurement of the event onset time is likely minimal. Selection bias resulting from loss to follow-up is not expected to influence our results because loss to follow-up was most likely nondifferential to participants' exposure at baseline and diabetes status during follow-up. Furthermore, excluding participants with prevalent diabetes at baseline was necessary to assess the influence of O_3 on diabetes incidence. However, given the age range of our cohort at enrollment and that diabetes was already prevalent at baseline in one-third of our cohort, those who were diagnosed during follow-up may have been less susceptible to developing diabetes in general as well as possibly in relation to O_3 exposure. The possibility of reverse causation cannot be ruled out if participants' outdoor physical activity was increased to successfully counteract elevated blood glucose levels prior to enrollment. But such countermeasures as treatments of high glucose levels would likely only follow a diabetes diagnosis, which would have been reported at baseline. In this study, we did not have time-varying physical activity information and we lacked the location information for the physical activities, thus the possibility of misclassification of physical activity level cannot be ruled out. However, there was no indication for effect measure modification of the association between O_3 and incident diabetes when using physical activity level based on indoor activities. This indicates that the increased risk of diabetes among those with higher levels of outdoor leisure-time physical activity did not simply reflect an effect of higher physical activity in general but, rather, specifically for outdoor activity. In addition, although most of the participants were already retired at baseline, some participants might have continued to work, including holding outdoor occupations during follow-up. Thus, it is possible that some of the observed effect measure modification might be partially attributable to outdoor occupational activities.

Conclusion

Our study results suggest that O_3 exposure increases the risk of diabetes among older Mexican Americans, particularly among those with higher levels of leisure-time outdoor physical activity. These findings are of great relevance for public health protection. Policies and strategies are needed to reduce O_3 exposure in communities to guarantee that the health benefits from physical activity are not diminished by O_3 pollution exposure, especially in vulnerable populations.

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